REMARKS/ARGUMENTS

Claims 1-25 were pending. Claims 2, 3, 9, 10, 13, 14, 19 and 20 are herein canceled without prejudice. Claims 1, 4-8, 11, 12, 15-18, 21 and 22 are to be amended. Claims 26-34 are newly presented. After entry of these amendments, claims 1, 4-8, 11, 12, 15-18, and 21-34 will be pending.

Claims 11-25 stand rejected for an alleged want of written description with respect to the description of 'proliferative disorders.'

Claims 11-25 stand rejected for an alleged want of enablement.

Claims 1-25 stand rejected under 35 U.S.C. §103 as allegedly obvious in view of Flygare et al. (U.S. Patent No. 6,482,680 B1).

Claims 1, 2, 6-13, 17-19 and 23-25 stand rejected for an alleged noncompliance with the judicially created doctrine of obviousness-type double patenting in view of U.S. Patent No. 6,355,628.

Applicants respond to these rejections below.

Support for the Amendments

Claims 1 and 17 are to be amended to recite the three formulae set forth in original claims 12 and 18.

Methods claims 11 and 17 are to be amended to set forth cancer as the proliferative disorder. Support for this subject matter is found in Figures 1 and 2 and in the specification at p. 2 in the first sentence of the Summary.

Claims 1 and 17 are each to be amended to set forth paclitaxel and gemcitabine as the antineoplastic agents Support for this subject matter is found in *inter alia* original claims 5 and 22 respectively and in Figures 1 and 2.

Claims 4, 15, and 21 are each to be amended to set forth paclitaxel as the antineoplastic agent. Support for this subject matter is found in *inter alia* the original version of each claim and in Figure 2.

Claims 5, 16, and 22 are each to be amended to set forth gemcitabine as the antineoplastic agent. Support for this subject matter is found in *inter alia* the original version of each claim and in Figure 1.

Claims 6, 7, and 8 are to be amended to set forth a different one of the three formulae set forth in claim 1. Support for this subject matter is *inter alia* as above for claim 1.

Claim 8 is also to be amended to correct a grammatical error. To fit the plural predicate of the verb "to be", the claim was amended to recite "are" in place of "is." Support for the subject matter of the claim is *inter alia* as set forth for the previous version of claim 8.

Claims 12 and 18 are each to be amended to set forth only the first member of the three formulae set forth in the previous version of each claim. These claims further set forth that the second agent is gemcitabine. Support for this subject matter is found *inter alia* in the previous version of these claims and as provided above for claims 5, 16, and 22.

New claims 26 and 28 set forth mammary cancer. Support for such subject matter is found in the specification, *inter alia*, in Figs. 1 and 2 and the last paragraph of p. 3.

New claims 27 and 29 set forth the subject is human. Support for such subject matter is found in the specification *inter alia* in the paragraph bridging pp. 9 and 10.

New claims 30 and 31 depend from claim 11 and set forth a different one of the formulae of claim 1. These claims further set forth the second antineoplastic agent is gemcitabine. Support is found as set forth above for claim 1 and claims 5-7.

New claims 32 and 33 depend from claim 17, and set forth a different one of the three formulae of claim 17. These claims further set forth the second antineoplastic agent is gemcitabine. Support is found as set forth above for claim 17 and claims 5-7.

New claim 34 depends from claim 8 and sets forth the antineoplastic agent is gemcitabine. Support for this subject matter is found in Figure 1.

In view of the above, Applicants believe the amendments to the claims add no new matter and respectfully request their entry.

Response to the Written Description Rejection of Claims 11-25

The Examiner considered the term 'proliferative disorders' to be inadequately supported by the specification. Without acquiescing to the position of the Examiner and in order to expedite prosecution of the present application, applicants have amended base claims 11 and 17 to remove the recital of 'proliferative disorders' and to recite therefor 'cancer.'

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Response to the Rejection of Claims 11-25 as Allegedly not Enabled Pursuant to 35 U.S.C. §112, 1st paragraph

As noted by the Examiner, whether undue experimentation[1] is required to practice an invention is typically determined by evaluating: (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Applicants address each of these factors and the Examiner's concerns as to each in turn.

i. Relative Skill of those in the Art.

Applicants agree with the Examiner that the relative skill of those in the art is high.

ii. Nature of the Invention.

The field of the invention is in the pharmaceutical arts and more particularly the chemotherapeutic field. The invention is drawn to subject matter related to combination cancer

[1] That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation' " in determining whether pending claims are enabled. *In re: Wands*, 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

chemotherapy using either gemcitabine or paclitaxel and a compound, or a pharmaceutically acceptable salt thereof, of one of several specified formulae. It is a field in which it is routine to screen a large number of compounds and compositions for their biological activity. It is a field in which the courts have held that the necessary showing for enablement does not require testing in humans[2].

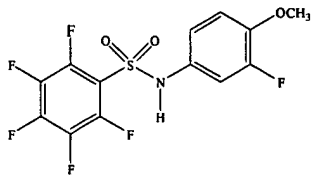
iii. Breadth of the Claims.

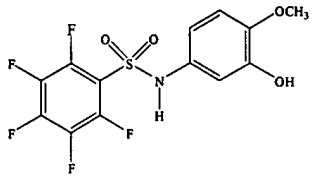
Without acquiescing to the position of the Examiner and in order to expedite prosecution of the present application, applicants have amended the base claims to remove the recital of 'proliferative disorders' and to recite therefor 'cancer.' Applicants have further amended the base claims to recite "an antineoplastic agent selected from the group consisting of paclitaxel and gemcitabine." Applicants have also further amended the base claims so that they are drawn in part to only three compounds of the original Formula I and their pharmaceutically acceptable salts.

Claim 17, for instance, has been amended to recite:

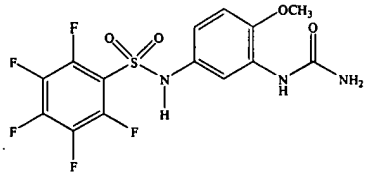
> A method for the treatment of cancer, said method comprising administering to a subject in need of such treatment:
>
> i) a first amount of an antineoplastic agent selected from the group consisting of paclitaxel and gemcitabine; and
>
> ii) a second amount of a compound of formula:

[2] *See Scott v. Finney,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").





or



and the pharmaceutically acceptable salts thereof;

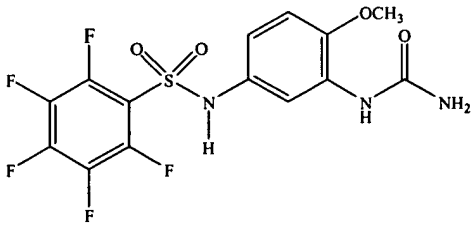
wherein said first amount and said second amount, in combination, are effective to treat said cancer.

iv. Amount of Guidance Presented.

Applicants teach all the methods required to practice the claimed subject matter. Methods of combination therapy are disclosed at p. 13-16 of the present specification. Moreover, as recited in the MPEP §2164.01 "A patent need not teach, and preferably omits, what is well known in the art."

v. Presence of Working Examples.

The specification provides working examples using an *in vivo* mammalian model for anticancer therapy for combinations of both gemcitabine and paclitaxel with a compound of the formula:



(Compound 2).

In particular, dose-response relationships for the compound in combination with either gemcitabine or paclitaxel are disclosed, respectively, in Figs. 1 and 2.

vi. State of the Art.

The state of the art is high and advanced in this particular subfield. Assays for screening carcinogens in animal models *in vitro* and *in vivo* are well known in the art as evidenced in the art cited by the Examiner. WO 00/61142, for instance, discloses a number of such assays. As to the subfield, WO 98/05315 (cited at p. 9, line 20 and enclosed with the Supplemental IDS) and incorporated by reference at p. 17, last paragraph, describes the activity of compounds of formula I in a variety of cancer bioassay systems. Paclitaxel and gemcitabine are also well known chemotherapeutic agents.

(vii) Predictability of the Art.

The Examiner challenged the predictability of the art with respect to the subject areas of 1) Treatment by Cancer Type and 2) Combination Chemotherapy. Applicants address these two subject areas in turn.

1. Treatment by Cancer Type

The Action cites *In re: Brana,* 34 USPQ2d 1436 (Fed. Cir. 1995) (enclosed) as supporting the following proposition:

> As discussed in the court in In re: Brana, 51 F.3d 1560 (Fed. Cir. 1995), in vitro assays are used by the NCI (such as the P388 and L1210 leukemia tests at issue therein) to measure the potential antitumor properties of a candidate compound. Brana at 1562-63. If success is shown in this initial screening step, this demonstrates that at least one cancer type (e.g., lymphocytic leukemia) is sensitive thereto and provides for the incentive to select it for further studies to determine its usefulness as a cancer therapeutic agent against other cancer types (lung, breast colon, etc.) id. at 1567-68. These in vitro tests are considered reasonably correlative of success *in vivo*.

However, *In re: Brana,* 51 F.3d 1560 (Fed. Cir. 1995) does not support the above proposition at all.

In contrast to the above proposition, the *Brana* decision is usually cited for the proposition that human clinical studies are not a requisite for patentability and that demonstrated activity in an acceptable experimental model is sufficient. *Brana* concerned the patentability of a

composition, not a method. The *Brana* court stated that it needed to find only enabled utility to support the composition claim. The *Brana* court indicated that it did not need to reach the question as to whether the antitumor activity data (i.e., *in vivo* efficacy test data for several of their compounds against two specific implanted murine lymphocytic leukemias, P388 and L1210) was predictive of therapeutic activity against other tumor types[3].

As the *Brana* court did not need to reach a decision as to whether the lymphocytic leukemia data was predictive of a generic anticancer activity, the alleged opinion as to such would be merely non-binding and non-precedential *dicta*. However, the *Brana* decision does not support even in *dicta* the rule that the Examiner would find there. Not once when discussing predictive value of the test data does the *Brana* decision appear to qualify its assessment of antitumoricity according to tumor type. For instance at p. 1443 the decision recites:

> Moreover, NCI apparently believes these tests are statistically significant because it has explicitly recognized both the P388 and L1210 murine tumor models as standard screening tests for determining whether new compounds may be useful as antitumor agents. [Brana at p. 1443]

Other references cited by the Examiner in the present Action are also opposite to the position of the Office Action. For instance, the Examiner cites a combination chemotherapy patent, U.S. Patent No. 6,465,448, in support of the position that subject matter of the claims is not enabled. However, this reference does not support the Examiner's position with respect to

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[3] As applicants point out, the P388 and L1210 cell lines, though technically labeled tumor models, were originally derived from lymphocytic leukemias in mice. Therefore, the P388 and L1210 cell lines do represent actual specific lymphocytic tumors; these models will produce this particular disease once implanted in mice. If applicants were required to wait until an animal naturally developed this specific tumor before testing the effectiveness of a compound against the tumor *in vivo*, as would be implied from the Commissioner's argument, there would be no effective way to test compounds *in vivo* on a large scale.

We conclude that these tumor models represent a specific disease against which the claimed compounds are alleged to be effective. Accordingly, in light of the explicit reference to Paull, applicants' specification alleges a sufficiently specific use. [*Brana* at p. 1441].

cancer types. While U.S. Patent No. 6,465,448 presented only animal model data concerning colon cancer, the patent nevertheless issued with a base claim which is *generic* as to cancer type:.

> 1. A method comprising:
>
> a) providing i) a patient diagnosed with cancer, ii) a first formulation comprising methoxyamine and iii) a second formulation comprising temozolomide;
>
> b) administering said first formulation to said patient; and
>
> c) administering said second formulation to said patient wherein methoxyamine is administered in an amount sufficient to potentiate toxicity of temozolomide.

Moreover, U.S. Patent No. 6,635,677 9 (enclosed) which is a divisional of the above patent issued October 21, 2003. The base claim of the '677 patent is also *generic* with respect to tumor type:

> 1. A method comprising:
>
> a) providing i) a patient diagnosed with cancer, ii) a first formulation comprising methoxyamine and iii) a second formulation comprising 1,3-bis(chloroethyl) 2-nitrosourea (BCNU);
>
> b) administering said first formulation to said patient; and
>
> c) administering said second formulation to said patient; wherein said methoxyamine is administered in an amount sufficient to potentiate toxicity of said BCNU.

In addition, U.S. Patent Nos. 6,355,628 and 6,482,860 which were cited by the Examiner against the present application also issued with base claims which were not limited to a single tumor type.

B. Combination Therapy

The Examiner cited both U.S. Patent No. 6,465,448 and the WO 00/61142 reference for the proposition that the interaction of chemotherapeutic agent combinations is hard to predict. The Action quoted the '448 patent thusly:

> The design of drug combinations for the chemotherapeutic treatment of cancer should be approached with the goals of 1) finding a combination that is synergistic with and not merely additive to the first compound with respect to the elimination of the tumor, and 2) finding a second drug that does not potentiate the toxic effects of the first chemotherapeutic agent. These conditions require a great deal of empirical testing of agents known to have anticancer properties with agents that either may have anticancer properties, or that may augment the first agent in other ways. TMZ is currently employed in chemotherapeutic treatment of certain tumors.

The Action further quoted the WO 00/61142 reference for the following proposition:

> Combination therapies, while desirable are a hit or miss proposition. The treatments are typically not additive. In many cases, cross effects and treatment load can result in lower effectiveness for the combinations, than either treatment alone...

In response, Applicants first note that the base claims have been amended to recite "an antineoplastic agent selected from the group consisting of paclitaxel and gemcitabine." Thus, the base claims recite particular antineoplastic agents which have been shown to be at least additive with Compound 2 (see Figures 1 and 2). As a result, lower dosages of each compound can be administered. Applicants thus believe the amendments to the base claims render the instant concern moot.

With respect to the second issue related to toxicity, safety is not a criterion of patentability. The Courts have long held that phase II clinical testing - which largely concerns safety - is not a criterion for whether a compound is patentable.[4]

---

[4] On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. *See* 21 U.S.C. Section 355(i)(1); 5 C.F.R. Section 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. *See* 21 C.F.R. Section 312.21(b)..[Brana at 1443].

viii. Quantity of Experimentation Necessary.

The field of the invention is the pharmaceutical arts. A great deal of experimentation is quite routine in this field. It is a field which is largely devoted to the screening and testing of a large number of candidate compounds, compositions and treatments in model systems[5]. In addition, as noted above, the Courts do not require clinical testing to demonstrate utility.

In fact very little additional experimentation would be required to practice other embodiments of the invention. The subject matter of the combination therapy is well exemplified in the specification. Methods of combination therapy using either gemcitabine and paclitaxel and Compound 2 are well-exemplified in Figs. 1 and 2. The subject matter of the other closely similar compounds of the claims is thus well supported in the instant specification.

Overall Summary of the Wands Analysis

Here,

(i) the relative skill and experience of those in the art of cancer chemotherapeutics is generally quite high;

(ii) the nature of the invention involves testing combinations of chemotherapeutic agents in model test systems which are well known in the art.

(iii) the breadth of the claims is completely commensurate with the specification disclosure, in particular, in view of the amendments, a greatly reduced number of possible combinations of agents are involved;

(iv) the specification provides adequate guidance for all manipulations required to practice the invention;

(v) the specification provides working examples;

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[5] Indeed, The Federal Circuit has held that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)(enclosed).

(vi) the state of the art is high, involving combinations which are limited in number and clearly set forth in the claims;

(vii) noting that FDA standards as to operability are not those set forth for patentability, the art is sufficiently predictable such that one of ordinary skill in the art would consider the disclosed data to support the operability of the claimed subject matter;

(viii) while the field of art is one in which a great deal of experimentation is routinely performed by a person of ordinary skill in the art, in fact relatively little additional research would be required to practice the invention.

In view of the above, Applicants believe that one of ordinary skill in the art could readily practice the invention as claimed using an amount of experimentation which would be clearly routine in the art. Applicants therefore request that the above rejection be reconsidered and withdrawn.

Response to the Rejection of Claims 1-24 under 35 U.S.C. §103(a) over Flygare et al. (U.S. Patent No. 6,482,860.

Without acquiescing to the position of the Examiner, Applicants have amended the base claims to recite "an antineoplastic agent selected from the group consisting of paclitaxel and gemcitabine." The specification in Figures 1 and 2 shows the substantially greater efficacy obtained in the subject animal tumor model when a subject compound of Formula I is used with gemcitabine (Figure 1) or paclitaxel (Figure 2).

With respect to claims 5, 12, 16, 18, 22, and 30 -34, in particular, these claims are drawn in part to subject matter wherein the antineoplastic agent is gemicitabine. The '860 patent does not appear to disclose gemcitabine.

With respect to claims 8, 31, 32, and 34, in particular, these claims are drawn in part to subject matter wherein the compound is Compound 2 or a pharmaceutically acceptable salt thereof. The '860 patent does not appear to disclose Compound 2.

With respect to claims 31, 32, and 34, in particular, these claims are drawn to in part to subject matter of gemcitabine which does not appear to be disclosed in the '860 patent and

to be drawn in part to subject matter of Compound 2 which does not appear to be disclosed in the '860 patent.

In view of the above, Applicants request that the above rejections be reconsidered and withdrawn.

Response to the Rejection of Claims 1, 2, 6-13, 17-19 and 23-25 for Alleged Obviousness-type Double Patenting in view of U.S. Patent No. 6,355,628.

The base claims have been amended to recite "an antineoplastic agent selected from the group consisting of paclitaxel and gemcitabine." The claims of the '628 patent in contrast recite "an antineoplastic coordination complex."

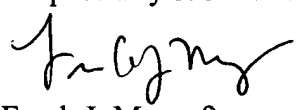
In view of the above, the Applicants respectfully request the above rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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FULL TEXT OF CASES (USPQ2D)
All Other Cases
In re Brana (CA FC) 34 USPQ2d 1436 (3/30/1995)

In re Brana (CA FC) 34 USPQ2d 1436

In re Brana

U.S. Court of Appeals Federal Circuit
34 USPQ2d 1436

Decided March 30, 1995
No. 93-1393

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Headnotes

PATENTS

1. Patentability/Validity -- Utility (§ 115.10)

Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Application for pharmaceutical invention did not fail to disclose specific disease against which claimed compounds are useful, and thereby fail to satisfy enablement requirement of 35 USC 112, since specification, which favorably compares compounds of invention with known compounds found to be highly effective against lymphocytic leukemia tumor models, implicitly asserts that claimed compounds are also highly effective against those models, and since tumor models are cell lines representing specific lymphocytic tumors.

2. Patentability/Validity -- Utility (§ 115.10)

Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Patent and Trademark Office improperly rejected, for lack of utility, application claims for pharmaceutical compounds used in cancer treatment in humans, since neither nature of invention nor evidence proferred by PTO would cause one of ordinary skill in art to reasonably doubt asserted utility, and since even if utility of compounds could be reasonably questioned, evidence that compounds within scope of claims, and other structurally similar compounds, are effective as chemotherapeutic agents in animals would be sufficient to convince one skilled in art of asserted utility; absence of evidence that claimed compounds have chemotherapeutic effect in humans does not warrant contrary conclusion, since proof of alleged pharmaceutical property for compound by statistically significant tests using standard experimental animals is sufficient to establish utility.

Case History and Disposition:

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application of Miguel F. Brana, Jose M.C. Berlanga, Marina M. Moset, Erich Schlick and Gerhard Keilhauer, serial no. 07/533,944, filed June 4, 1990, which is a continuation of serial no. 213,690, filed June 30, 1988. From decision upholding examiner's rejection of claims 10-13, applicants appeal. Reversed.

Attorneys:
Malcolm J. MacDonald, Herbert B. Keil, and David S. Nagy, Washington, D.C., for appellants.

Fred E. McKelvey, Solicitor, PTO; Albin F. Drost, Deputy Solicitor; Richard E. Schafer, Teddy S. Gron, Joseph G. Piccolo and Richard L. Torczon, Associate Solicitors, for appellee.

Judge:
Before Plager, Lourie, and Rader, circuit judges.

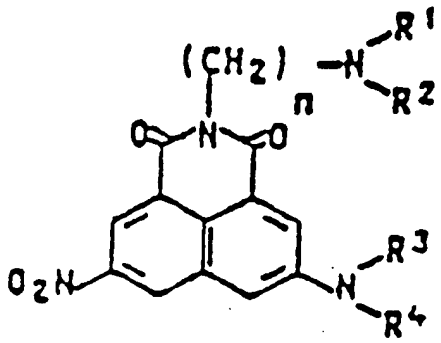
Opinion Text

Opinion By:
Plager, J.

Miguel F. Brana, *et al.* (applicants), appeal the March 19, 1993 decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), in Appeal No. 92-1196. The Board affirmed the examiner's rejection of claims 10-13 of patent application Serial No. 533,944 under 35 U.S.C. Section 112 Para.1 (1988). 1 The examiner's rejection, upon which the Board relied in rendering its decision, was based specifically on a challenge to the utility of the claimed compounds and the amount of experimentation necessary to use the compounds. We conclude the Board erred, and reverse.

I. BACKGROUND

On June 30, 1988, applicants filed patent application Serial No. 213,690 (the '690 application) 2 directed to 5-nitrobenzo [de]isoquinoline-1,3-dione compounds, for use as antitumor substances, having the following formula:



where n is 1 or 2, R [1] and R [2] are identical or different and are each hydrogen,

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C1-C6-alkyl, C1-C6-hydroxyalkyl, pyrrolidinyl, morpholino, piperidinyl or piperacinyl, and R [3] and R [4] are identical or different and are each hydrogen, C1-C6-alkyl, C1-C6-acyl, C2-C7-alkoxycarbonyl, ureyl, aminocarbonyl or C2-C7-alkylaminocarbonyl. These claimed compounds differ from several prior art benzo [de]isoquinoline-1,3-dione compounds due to the presence of a nitro group (O2N) at the 5-position and an amino or other amino group (NR [3]R [4]) at the 8-position of the isoquinoline ring. The specification states that these non- symmetrical substitutions at the 5- and 8-positions produce compounds with "a better action and a better action spectrum as antitumor substances" than known benzo [de]isoquinolines, namely those in K.D. Paull et al., *Computer Assisted Structure- Activity Correlations, Drug Research, 34(II),* 1243-46 (1984) (Paull). Paull describes a computer-assisted evaluation of benzo [de]isoquinoline-1,3-diones and related compounds which have been screened for antitumor activity by testing their efficacy *in vivo* 3 against two specific implanted murine (i.e., utilizing mice as test subjects) lymphocytic leukemias, P388 and L1210. 4 These two *in vivo* tests are widely used by the National Cancer Institute (NCI) to measure the antitumor properties of a compound. Paull noted that one compound in particular, benzo [de]isoquinoline-1,3(2H)dione,5-amino-2(2-dimethyl-aminoethyl [sic]) (hereinafter "NSC 308847"), was found to show excellent activity against these two specific tumor models. Based on their analysis, compound NSC 308847 was selected for further studies by NCI. In addition to comparing the effectiveness of the claimed compounds with structurally similar compounds in Paull, applicants' patent specification illustrates the cytotoxicity of the claimed compounds against human tumor cells, *in vitro,* 5 and concludes that these tests "had a good action." 6

The examiner initially rejected applicants' claims in the '690 application as obvious under 35 U.S.C. Section 103 in light of U.S. Patent No. 4,614,820, issued to and referred to hereafter as Zee-Cheng *et al.* Zee-Cheng *et al.* discloses a benzo [de]isoquinoline compound for use as an antitumor agent with symmetrical substitutions on the 5-position and 8-position of the quinoline ring; in both positions the substitution was either an amino or nitro group. 7 Although not identical to the applicants' claimed compounds, the examiner noted the similar substitution pattern (i.e., at the same positions on the isoquinoline ring) and concluded that a mixed substitution of the invention therefore would have been obvious in view of Zee-Cheng *et al.*

In a response dated July 14, 1989, the applicants rebutted the Section 103 rejection. Applicants asserted that their mixed disubstituted compounds had unexpectedly better antitumor properties than the symmetrically substituted compounds in Zee-Cheng *et al.* In support of this assertion applicants attached the declaration of Dr. Gerhard Keilhauer. In his declaration Dr. Keilhauer reported that his

tests indicated that applicants' claimed compounds were far more effective as antitumor agents than the compounds disclosed in Zee-Cheng *et al.* when tested, *in vitro,* against two specific types of human tumor cells, HEp and HCT-29. 8 Applicants further noted that, although the differences between the compounds in Zee-Cheng *et al.* and applicants' claimed compounds were slight, there was no suggestion in the art that these improved results (over Zee-Cheng *et al.*) would have been expected. Although the applicants overcame the Section 103 rejection, the examiner nevertheless issued a final rejection, on different grounds, on September 5, 1989.

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On June 4, 1990, applicants filed a continuation application, Serial No. 533,944 (the '944 application), from the above-mentioned '690 application. Claims 10-13, the only claims remaining in the continuation application, were rejected in a final office action dated May 1, 1991. Applicants appealed the examiner's final rejection to the Board.

In his answer to the applicants' appeal brief, the examiner stated that the final rejection was based on 35 U.S.C. Section 112 Para.1. 9 The examiner first noted that the specification failed to describe any specific disease against which the claimed compounds were active. Furthermore, the examiner concluded that the prior art tests performed in Paull and the tests disclosed in the specification were not sufficient to establish a reasonable expectation that the claimed compounds had a practical utility (i.e. antitumor activity in humans). 10

In a decision dated March 19, 1993, the Board affirmed the examiner's final rejection. The three-page opinion, which lacked any additional analysis, relied entirely on the examiner's reasoning. Although noting that it also would have been proper for the examiner to reject the claims under 35 U.S.C. Section 101, the Board affirmed solely on the basis of the Examiner's Section 112 Para.1 rejection. This appeal followed.

II. DISCUSSION

At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago. 11 We note the Commissioner has recently addressed this question in his Examiner Guidelines for Biotech Applications, *see* 60 Fed. Reg. 97 (1995); 49 Pat. Trademark & Copyright J. (BNA) No. 1210, at 234 (Jan. 5, 1995).

The requirement that an invention have utility is found in 35 U.S.C. Section 101: "Whoever invents . . . any new and *useful* . . . composition of matter . . . may obtain a patent therefor. . . ." (emphasis added). It is also implicit in Section 112 Para.1, which reads:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As noted, although the examiner and the Board both mentioned Section 101, and the rejection appears to be based on the issue of whether the compounds had a practical utility, a Section 101 issue, the rejection according to the Board stands on the requirements of Section 112 Para.1. It is to that provision that we address ourselves. 12 The Board gives two reasons for the rejection; 13 we will consider these in turn.

1.

The first basis for the Board's decision was that the applicants' specification failed to disclose a specific disease against which the

claimed compounds are useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.* , 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987). In support, the Commissioner argues that the disclosed uses in the '944 application, namely the "treatment of diseases" and "antitumor substances," are similar to the nebulous disclosure found insufficient in *In re Kirk,* 376 F.2d 936, 153 USPQ 48 (CCPA 1967). This argument is not without merit.

In *Kirk* applicants claimed a new class of steroid compounds. One of the alleged utilities disclosed in the specification was that these compounds possessed "high biological activity." *Id.* at 938, 153 USPQ at 50. The specification, however, failed to disclose which biological properties made the compounds useful. Moreover, the court found that known specific uses of similar compounds did not cure this defect since there was no disclosure in the specification that the properties of the claimed compounds were the same as those of the known similar compounds. *Id.* at 942, 153 USPQ at 53. Furthermore, it was not alleged that one of skill in the art would have known of any specific uses, and therefore, the court concluded this alleged use was too obscure to enable one of skill in the art to use the claimed invention. *See also Kawai v. Metlesics,* 480 F.2d 880, 178 USPQ 158 (CCPA 1973).

[1] *Kirk* would potentially be dispositive of this case were the above-mentioned language the only assertion of utility found in the '944 application. Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, *see supra* note 4, Paull grouped various benzo [de]isoquinoline-1,3-diones, which had previously been tested *in vivo* for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, 14 applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this particular type of cancer is much more specific than the vaguely intimated uses rejected by the courts in *Kirk* and *Kawai. See, e.g., Cross v. Iizuka,* 753 F.2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes -- sufficiently specific to satisfy the threshold requirement in *Kirk* and *Kawai.*)

The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

As applicants point out, the P388 and L1210 cell lines, though technically labeled tumor models, were originally derived from lymphocytic leukemias in mice. Therefore, the P388 and L1210 cell lines do represent actual specific lymphocytic tumors; these models will produce this particular disease once implanted in mice. If applicants were required to wait until an animal naturally developed this specific tumor before testing the effectiveness of a compound against the tumor *in vivo,* as would be implied from the Commissioner's argument, there would be no effective way to test compounds *in vivo* on a large scale.

We conclude that these tumor models represent a specific disease against which the claimed compounds are alleged to be effective. Accordingly, in light of the explicit reference to Paull, applicants' specification alleges a sufficiently specific use.

2.

The second basis for the Board's rejection was that, even if the specification did allege a specific use, applicants failed to prove that the claimed compounds are useful. Citing various references, 15 the

Board found, and the Commissioner now argues, that the tests offered by the applicants to prove utility

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were inadequate to convince one of ordinary skill in the art that the claimed compounds are useful as antitumor agents. 16

This court's predecessor has stated:

[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of Section 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. *Id.* at 224, 169 USPQ at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Bundy,* 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981). 17

[2] The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, 18 do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness.

The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Jolles,* 628 F.2d at 1327, 206 USPQ at 890. Modern science has previously identified numerous successful chemotherapeutic agents. In addition, the prior art, specifically Zee Cheng *et al.* , discloses structurally similar compounds to those claimed by the applicants which have been proven *in vivo* to be effective as chemotherapeutic agents against various tumor models.

Taking these facts -- the nature of the invention and the PTO's proffered evidence -- into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. *See In re Marzocchi,* 439 F.2d at 224, 169 USPQ at 370.

We do not rest our decision there, however. Even if one skilled in the art would have reasonably questioned the asserted utility, i.e., even if the PTO met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility. In particular, applicants provided through Dr. Kluge's declaration 19 test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor

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model *in vivo.* Such evidence alone should have been sufficient to satisfy applicants' burden.

The prior art further supports the conclusion that one skilled in the art would be convinced of the applicants' asserted utility. As previously mentioned, prior art -- Zee Cheng *et al.* and Paull -- disclosed structurally similar compounds which were proven *in vivo* against various tumor models to be effective as chemotherapeutic agents. Although it is true that minor changes in chemical compounds can radically alter their effects on the human body, *Kawai,* 480 F.2d at 891, 178 USPQ at 167, evidence of success in structurally similar compounds is relevant in determining whether one skilled in

the art would believe an asserted utility. *See Rey-Bellet v. Engelhardt,* 493 F.2d 1380, 181 USPQ 453 (CCPA 1974); *Kawai,* 480 F.2d 880, 178 USPQ 158 .

The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. 20 The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings."). Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. *In re Krimmel,* 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); *see also In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961). In concluding that similar *in vivo* tests were adequate proof of utility the court in *In re Krimmel* stated:

We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

Krimmel, 292 F.2d at 953, 130 USPQ at 219. Moreover, NCI apparently believes these tests are statistically significant because it has explicitly recognized both the P388 and L1210 murine tumor models as standard screening tests for determining whether new compounds may be useful as antitumor agents.

In the context of this case the Martin and Pazdur references, on which the Commissioner relies, do not convince us otherwise. Pazdur only questions the reliability of the screening tests against lung cancer; it says nothing regarding other types of tumors. Although the Martin reference does note that some laboratory oncologists are skeptical about the predictive value of *in vivo* murine tumor models for human therapy, Martin recognizes that these tumor models continue to contribute to an increasing human cure rate. In fact, the authors conclude that this perception (i.e. lack of predictive reliability) is not tenable in light of present information.

On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. *See* 21 U.S.C. Section 355(i)(1); 5 C.F.R. Section 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. *See* 21 C.F.R. Section 312.21(b).

FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the

associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

In view of all the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. Section 112 Para.1.

3.

The Commissioner takes this opportunity to raise the question of this court's standard of review when deciding cases on appeal from the PTO. Traditionally we have recited our standard of review to be, with regard to questions of law, that review is without deference to the views of the Agency, *In re Donald son,* 16 F.3d 1189, 1192, 29 USPQ2d 1845, 1848 (Fed. Cir. 1994) (in banc), *In re Caveney,* 761 F.2d 671, 674, 226 USPQ 1, 3 (Fed. Cir. 1985), and with regard to questions of fact, we defer to the Agency unless its findings are "clearly erroneous." *See, e.g., In re Baxter Travenol Labs,* 952 F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990); *In re De Blauwe,* 736 F.2d 699, 222 USPQ 191 (Fed. Cir. 1984).

With regard to judgment calls, those questions that fall " [s]omewhere near the middle of the fact-law spectrum," this court has recognized "the falseness of the fact-law dichotomy, since the determination at issue, involving as it does the application of a general legal standard to particular facts, is probably most realistically described as neither of fact nor law, but mixed." *Campbell v. Merit Systems Protection Board,* 27 F.3d 1560, 1565 (Fed. Cir. 1994). When these questions of judgment are before us, whether we defer, and the extent to which we defer, turns on the nature of the case and the nature of the judgment. *Id.* ("Characterization therefore must follow from an *a priori* decision as to whether deferring . . . is sound judicial policy. We would be less than candid to suggest otherwise.").

The Commissioner contends that the appropriate standard of review for this court regarding questions of law, of fact, and mixed questions of law and fact, coming to us from the PTO is found in the Administrative Procedure Act (APA) at 5 U.S.C. Section 706. The standard set out there is that " [t]he reviewing court shall . . . hold unlawful and set aside agency action, findings, and conclusions found to be -- (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law; . . . (E) unsupported by substantial evidence. . . ." The Commissioner is of the view that the stated standard we now use, which is the traditional standard of review for matters coming from a trial court, is not appropriate for decisions coming from an agency with presumed expertise in the subject area, and is not in accord with law. 21

Applicants argue that by custom and tradition, recognized by the law of this court, the standard of review we have applied, even though inconsistent with the standard set forth in the APA, nevertheless is a permissible standard. In our consideration of this issue, there is a reality check: would it matter to the outcome in a given case which formulation of the standard a court articulates in arriving at its decision? The answer no doubt must be that, even though in some cases it might not matter, in others it would, otherwise the lengthy debates about the meaning of these formulations and the circumstances in which they apply would be unnecessary.

A preliminary question, then, is whether this is one of those cases in which a difference in the standard of review would make a difference in the outcome. The ultimate issue is whether the Board correctly applied the Section 112 Para.1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of Section 101, to the facts of this case. As we have explained, the issue breaks down into two subsidiary issues: (1) whether a person of ordinary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a requirement that makes human testing a prerequisite to patentability under the circumstances of this case.

The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in

the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from

the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious decision.
The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.
If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

III. CONCLUSION

The Board erred in affirming the examiner's rejection under 35 U.S.C. Section 112 Para.1. The decision is reversed. *REVERSED* .

Footnotes

Footnote 1. Unless otherwise noted, all United States Code citations are to the 1988 edition.
Footnote 2. This is a divisional of patent application Serial No. 110,871 filed October 21, 1987.
Footnote 3. *In vivo* means " [i]n the living body, referring to a process occurring therein." *Steadman's Medical Dictionary* 798 (25th ed. 1990). *In vitro* means " [i]n an artificial environment, referring to a process or reaction occurring therein, as in a test tube or culture media." *Id.*
Footnote 4. The analysis in Paull consisted of grouping the previously-tested compounds into groups based on common structural features and cross- referencing the various groups, in light of the success rates of the group as a whole, to determine specific compounds that may be effective in treating tumors.
Footnote 5. *See supra* note 3.
Footnote 6. The specification does not state the specific type of human tumor cells used in this test.
Footnote 7. The chemical compound in Zee-Cheng *et al.* is labeled a 3,6-disubstituted-1,8-naphthalimide and uses different numbering for the positions on the isoquinoline ring. The structure of this compound, however, is identical to that claimed by the applicants except for symmetrical substitutions at the 5-position and the 8-position of the isoquinoline ring. Zee-Cheng *et al.* teaches identical substitutions of amino or nitro groups while applicants claim a nitro group substitution at the 5-position and an amino group substitution at the 8-position.
Footnote 8. HEp cells are derived from laryngeal cancer and HCT-29 cells from colon cancer.
Footnote 9. The examiner's answer noted that the final rejection also could have been made under 35 U.S.C. Section 101 for failure to disclose a practical utility.
Footnote 10. The examiner subsequently filed two supplemental answers in response to arguments raised by the applicants in supplemental reply briefs.
Footnote 11. *See, e.g., Cross v. Iizuka,* 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Langer,* 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Krimmel,* 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961).
Footnote 12. This court's predecessor has determined that absence of utility can be the basis of a rejection under both 35 U.S.C. Section 101 and Section 112 Para.1. *In re Jolles,* 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche,* 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971) (" [I]f such compositions are in fact useless, appellant's specification cannot have taught how to use them."). Since the Board affirmed the examiner's rejection based solely on Section 112 Para.1, however, our review is limited only to whether the application complies with Section 112

Para.1.

Footnote 13. The Board's decision did not expressly make any independent factual determinations or legal conclusions. Rather, the Board stated that it "agree [d] with the examiner's well reasoned, well stated and fully supported by citation of relevant precedent position in every particular, and any further comment which we might add would be redundant." *Ex parte Brana et al.* , No. 92-1196 (Bd. Pat. App. & Int. March 19, 1993) at 2-3. Therefore, reference in this opinion to Board findings are actually arguments made by the examiner which have been expressly adopted by the Board.

Footnote 14. Paull also found NSC 308847 to be effective against two other test models, B16 melanoma and Colon C872.

Footnote 15. *See* Pazdur et al., *Correlation of Murine Antitumor Models in Predicting Clinical Drug Activity in Non-Small Cell Lung Cancer: A Six Year Experience,* 3 *Proceedings Am. Soc. Clin. Oncology* 219 (1984); Martin et al., *Role of Murine Tumor Models in Cancer Research,* 46 *Cancer Research* 2189 (April 1986).

Footnote 16. As noted, this would appear to be a Section 101 issue, rather than Section 112.

Footnote 17. *See also In re Novak,* 306 F.2d 924, 928, 134 USPQ 335, 337 (CCPA 1962) (stating that it is proper for the examiner to request evidence to substantiate an asserted utility unless one with ordinary skill in the art would accept the allegations as obviously valid and correct); *In re Chilowsky,* 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956) (" [W]here the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry . . . no further evidence is required."). *But see In re Marzocchi,* 439 F.2d at 223, 169 USPQ at 369-70 ("In the field of chemistry generally there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles.").

Footnote 18. *See supra* note 15.

Footnote 19. The declaration of Michael Kluge was signed and dated June 19, 1991. This declaration listed test results (i.e. antitumor activity) of the claimed compounds, *in vivo,* against L1210 tumor cells and concluded that these compounds would likely be clinically useful as anti-cancer agents. Enablement, or utility, is determined as of the application filing date. *In re Glass,* 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974). The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi,* 439 F.2d at 224 n.4, 169 USPQ at 370 n.4. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility).

Footnote 20. We note that this discussion is relevant to the earlier discussion as well. If we were to conclude that these *in vivo* tests are insufficient to establish usefulness for the claimed compounds, that would bear on the issue of whether one skilled in the art would, in light of the structurally similar compounds in Paull and Zee Cheng *et al.* , have cause to doubt applicants' asserted usefulness for the compounds.

Footnote 21. Congress enacted the Administrative Procedure Act (APA) on June 11, 1946. *See* 1 *Kenneth Culp Davis, Administrative Law Treatise,* Section 1:7 (2d ed. 1978). The APA sets forth a framework for administrative agency procedure and provides judicial review for persons adversely affected by final agency actions. Chapter 7, codified at 5 U.S.C. Sections 701-706, contains the APA judicial review provisions, including the standard of review provision quoted above.

- End of Case -

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FULL TEXT OF CASES (USPQ2D)
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U.S. v. Telectronics Inc. (CA FC) 8 USPQ2d 1217 (9/22/1988)

U.S. v. Telectronics Inc. (CA FC) 8 USPQ2d 1217

U.S. v. Telectronics Inc.

U.S. Court of Appeals Federal Circuit
8 USPQ2d 1217

Decided September 22, 1988
Nos. 87-1445, -1446

Headnotes

PATENTS

1. Patent construction -- Claims -- Broad or narrow (§ 125.1303)

Federal district court erred in interpreting claim for bone growth stimulator device by limiting claim to non-implanted anodes and excluding anodes implanted adjacent to bone and by basing interpretation on claim language which cautions against formation of "fibrous tissue" around anode, since such language is not determinative of anode placement.

2. Patent construction -- Claims -- Broad or narrow (§ 125.1303)

Doctrine of claim differentiation presumes difference in meaning and scope when different words or phrases are used in separate claims, and thus federal district court erroneously construed claim of bone healing invention so that its limitations are same as dependent claim.

3. Infringement -- Literal infringement (§ 120.05)

Determination that claims for patented bone growth stimulator device, as properly construed, encompass both skin anode and implanted anode warrants finding of literal infringement by defendant's device, in view of defendant's admission that literal infringement is avoided only if patented device's claims are construed to be limited to skin anode.

4. Patentability/Validity -- Adequacy of disclosure (§ 115.12)

Patent infringement defendant which seeks to prove invalidity based upon non-enablement must show facts, supported by clear and convincing evidence, demonstrating that patent was not enabling, and federal district court findings that claims for patented bone growth stimulator device are not limited to specific metal/current combination, and that determination of optimal electrical current for materials other than stainless steel would require dose response study and would involve "undue amount of experimentation," are insufficient to establish clear and convincing proof of invalidity, since time and cost of such studies do not, standing alone, show experimentation to be excessive.

Particular patents -- General and mechanical -- Medical healing device

3,842,841, Brighton, Friedenberg, and Redka, constant current power pack for expediting healing of bone fracture and bone defects in living beings, including means of internal implant, and method of using device, valid and infringed.

Case History and Disposition:

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Appeal from the U.S. District Court for the District of Colorado, Matsch, J; 3 USPQ2d 1571.

Page 1218

Patent infringement action brought by U.S. and Zimmer Inc., as involuntary plaintiff, against Telectronics Inc. and BGS Medical Inc. From federal district court's judgment holding that defendants did not infringe, that patent is not invalid under 35 USC 112, and holding that defendant Telectronics is not entitled to attorney's fees, parties cross-appeal. Affirmed in part and reversed in part.

Attorneys:
John Fargo (Richard K. Willard, assistant attorney general and Vito J. DiPietro, with him on brief), Department of Justice, for plaintiff/appellant.

Michael I. Rackman, of Gottlieb, Rackman & Reisman, New York, N.Y. (Barry A. Cooper and Jeffrey M. Kaden, New York, and William C. Nealon, Suffield, Conn., with him on brief), for defendants/counterclaim-plaintiffs/cross-appellants.

Judge:
Before Newman, Archer, and Mayer, circuit judges.

Opinion Text

Opinion By:
Archer, J.

The United States of America (government) appeals the judgment of the United States District Court for the District of Colorado in *United States v. Telectronics, Inc* ., 658 F.Supp. 579, 3 USPQ2d 1571 (D. Colo. 1987), holding that Telectronics, Inc. and BGS Medical, Inc. (Telectronics) do not infringe U.S. Patent No. 3,842,841 ('841). Telectronics cross-appeals the determinations that the '841 patent is not invalid under 35 U.S.C. §112 (1982) and that Telectronics is not entitled to attorney fees under 35 U.S.C. §285 (1982). 1 We reverse the district court's holding that the '841 patent is not infringed by Telectronics. The determinations that the patent is not invalid under section 112 and that Telectronics is not entitled to attorney fees are affirmed.

Background

The '841 patent issued to Carl T. Brighton, et al. and was assigned to the United States. The patent resulted from work under contract between the Office of Naval Research and the University of Pennsylvania, where the inventors were employed. 658 F.Supp. at 581, 3 USPQ2d at 1571. The '841 patent is directed to a bone growth stimulator device for speeding the healing of fractures and other bone defects. The accused devices of Telectronics are marketed under the name OSTEOSTIM and include Model 2000 and earlier models S-12, HS-12 and XM-12. Zimmer, Inc. (Zimmer), a licensee of the government under the '841 patent, also markets a bone growth stimulator which the district court found to be "quite similar to the preferred embodiment of the invention shown in the patent." 658 F.Supp. at 581, 3 USPQ2d at 1571.

Normally bone fractures heal naturally as a result of the body's own reparative process. Approximately five percent of the time, however, natural healing does not occur and bone grafting is conventionally employed to attempt to stimulate further reparative growth. 658 F.Supp. at 581-82, 3 USPQ2d at 1572. Bone growth stimulators are particularly useful in the treatment of fractures normally requiring grafting. The success rate is at least as great as with grafting and the procedure results in less discomfort to the patient. 658 F.Supp. at 582, 3 USPQ2d at 1572. Bone growth stimulators expedite the healing of a fracture or bone defect by passing a low level constant direct current to the site of the fracture via a cathode placed internally at the site of the fracture. *Id* . The placement of the circuit-completing anode is at issue in this case.

The claim of the '841 patent at issue reads:

1. A system for expediting the healing of bone fractures and bone defects in a living being comprising:
constant current source means for providing a constant value of current despite changes in load;
means for connecting said constant current means to the living being, such connection acting to produce current flow into said fracture or defect,
said connecting means including further means for application internally of said living being at the fracture or defect site,
said constant current being a selected value within a predetermined microampere range so as to promote bone formation at the fracture or bone defect site and avoid fibrous tissue formation in other areas of the living being.

In describing the operation of the patented invention and the accused devices, the district court stated that

hen using the product of either party, the cathode (negative terminal) is placed in the defect site. The Zimmer cathode is made of stainless steel, the material described in the patent. The OSTEOSTIM cathode is made of titanium. The major

difference between the products of the parties pertains to the anode (positive terminal). As disclosed in the patent drawing and accompanying description, and as marketed by Zimmer, the anode is placed on the skin of the patient. So is the power pack (current source) itself. The only internal element [in Zimmer] is the cathode -- a pin which is inserted through the skin into the defect site. This technique

avoids the need for surgery; after several months of treatment, the cathode pin is simply pulled out. The OSTEOSTIM device, on the other hand, is completely implanted, an embodiment which while not shown in the patent drawing is nevertheless described. The power pack and the anode of the OSTEOSTIM are placed in soft tissue near the bone. The original OSTEOSTIM S-12 had a power pack from which two wires extended, the wires terminating respectively at a titanium cathode for placement in the defect site, and a platinum anode for placement in the soft tissue. In all of the later models, including the OSTEOSTIM-2000, the anode wire was omitted. The anode is the case itself -- titanium with a patch of platinum.
658 F.Supp. at 582, 3 USPQ2d at 1572.
Because the Telectronics devices have an implanted anode, the district court stated that "the critical question in the case is whether the language of claim 1 (and with it, the dependent claims) is limited to a skin anode." 658 F.Supp. at 583, 3 USPQ2d at 1573. Telectronics contended before the district court that "an internal anode could not come within the literal language of claim 1 because fibrous tissue formation inevitably results from such an implant." *Id* . In finding no literal infringement, the district court held with respect to the accused device that
fibrous tissue formation could not be avoided in the dictionary sense of "keep away from" or "stay clear of".
The claim limitation directed to the avoidance of fibrous tissue means what it plainly says. Accordingly, there is no literal infringement because in the context of the patent, even minimal fibrous tissue formation is not its avoidance. *Id* .
The district court also held that the '841 patent was not infringed under the doctrine of equivalents on the basis that the prosecution history established that the patentees, in responding to rejections by the examiner, repeatedly represented that the invention was limited to a surface or skin. anode. After examining the prosecution history in detail, the district court stated: "[i]t is clear from the file history that what convinced the Examiner to allow the claims over the prior art was the argument that a skin anode was used in the invention." 658 F.Supp. at 587, 3 USPQ2d at 1576.
On appeal, the government contends that the district court in its literal infringement analysis erred as a matter of law in its claim interpretation. According to the government, the claim limitation read as a whole requires the constant current supply to be controlled in a manner to minimize the amount of fibrous tissue formed. Telectronics counters that the district court properly interpreted the claim phrase "avoid fibrous tissue formation" and the prosecution history to find that the claim is limited to the use of a skin anode.

OPINION

1. *Claim Interpretation*

A. Analysis of literal infringement involves two inquiries: first the claims must be properly construed to determine their scope and then it must be determined whether the properly interpreted claims encompass the accused structure. *ZMI Corp. v. Cardiac Resuscitator Corp* ., 844 F.2d 1576, 1578, 6 USPQ2d 1557, 1559 (Fed. Cir. 1988). Claim construction is reviewed as a matter of law. However, interpretation of a claim may depend on evidentiary material about which there is a factual dispute, requiring resolution of factual issues as a basis for interpretation of the claim. *Uniroyal, Inc. v. Rudkin-Wiley Corp* ., 837 F.2d 1044, 1054, 5 USPQ2d 1434, 1441 (Fed. Cir. 1988). In interpreting claims resort should be made to the claims at issue, the specification, and the prosecution history. *Loctite Corp. v. Ultraseal Ltd* ., 781 F.2d 861, 867, 228 USPQ 90, 93 (Fed. Cir. 1985). The question of literal infringement is a factual inquiry and is reviewed on a clearly erroneous standard. *Loctite Corp* ., 781 F.2d at 866, 228 USPQ at 93.
B. The district court interpreted the phrase "avoid fibrous tissue formation" as precluding the use of an implanted anode, and thus limiting the claim to a surface or skin anode. To the court, the word "avoid" based on its dictionary definition meant that there could be no fibrous tissue. Because an implanted anode inevitably resulted in some fibrous tissue, the court determined that this placement of the anode was not covered by the claim language.

The government argues that the district court erred in its interpretation because the phrase at issue was not read in context. It contends that the claim language read as a whole only requires that there be avoidance

or minimization of fibrous tissue formation by controlling or selecting the current. Thus, any fibrous tissue that may result from the implantation of the anode is immaterial.

[1] We agree that the district court erred in its interpretation of the limitation of claim 1 and in its conclusion that such language is determinative of the anode placement. In the claim, constant current is a "selected value . . . so as to promote bone formation . . . and avoid fibrous tissue formation in other areas." Nothing in this language relates to fibrous tissue that may be formed from implantation of an anode. The plain meaning of the disputed language is only that current related fibrous tissue formation is to be avoided.

In considering other sources for interpretation of claims, we note that the specification supports the plain meaning of the clause at issue. *See Autogiro Co. of America v. United States* , 384 F.2d 391, 397, 155 USPQ 697, 702-03 (Ct. Cl. 1967) ("[p]atent law allows the inventor to be his own lexicographer. . . . [t]he specification aids in ascertaining the scope and meaning of the language employed in the claims inasmuch as words must be used in the same way in both the claims and the specification.") The specification makes no mention of whether a skin anode or an implanted anode may cause or deter the formation of fibrous tissue. There is, however, a discussion of the increase or decrease in fibrous tissue that is formed with varying currents. Further, we find nothing in the prosecution history that would indicate that fibrous tissue resulting from implantation of an electrode was at issue or was intended to be covered by the claim language.

The claim language relied on by the district court is, therefore, not determinative of anode placement and does not require that claim 1 be limited to a surface or skin anode.

C. Claim 1 recites a "means for connecting said constant current means to the living being, such connection acting to produce current flow into said fracture or defect." Since this recitation is in the "means plus function" format permitted by 35 U.S.C. §112, ¶6, it must be interpreted to cover the structure disclosed in the specification and the equivalents thereof. *See D.M.I. Inc. v. Deere & Co* ., 755 F.2d 1570, 1575, 225 USPQ 236, 239 (Fed. Cir. 1985).

"In construing a 'means plus function' claim, as also other types of claims, a number of factors may be considered, including the language of the claim, the patent specification, the prosecution history of the patent, other claims in the patent, and expert testimony [citations omitted]. Once such factors are weighed, the scope of the 'means' claim may be determined." *Palumbo v. Don-Joy Co* ., 762 F.2d 969, 975, 226 USPQ 5, 8 (Fed. Cir. 1985); *see also Moeller v. Ionetics Inc* ., 794 F.2d 653, 656, 229 USPQ 992, 994 (Fed. Cir. 1986) (resort to extrinsic evidence, such as the prosecution history, is necessary to interpret disputed claims); *SSIH Equip. S.A. v. U.S. Int'l Trade Comm'n* , 718 F.2d 365, 376, 218 USPQ 678, 688 (Fed. Cir. 1983) (the prosecution history is always relevant to proper claim interpretation). "[T]he prosecution history (or file wrapper) limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance." *Standard Oil Co. v. American Cyanamid Co* ., 774 F.2d 448, 452, 227 USPQ 293, 296 (Fed. Cir. 1985); *see also McGill Inc. v. John Zink Co* ., 736 F.2d 666, 673, 221 USPQ 944, 949 (Fed. Cir.), *cert. denied* , 469 U.S. 1037 (1984).

The district court found that both implanted and surface anodes are disclosed in the specification of the '841 patent. The specification provides: "[a]lthough the cathode must be placed in the fracture . . . the anode, though described as preferably being placed on the remote side of the site from the cathode, may be placed anywhere so long as it completes a circuit with the cathode." Elsewhere the specification provides that "[i]f the anode is to be implanted, it . . . is bared of its cover." Thus, unless other relevant claim interpretation factors clearly require a different construction, the plain language of claim 1 and the specification cover an implanted anode as well as a skin or surface anode.

In its claim construction and literal infringement analysis, the district court did not consider the prosecution history but concluded for the reasons indicated in I.A., *supra* , that a surface anode was required. The prosecution history, however, was extensively discussed in the court's consideration of the doctrine of equivalents.

Prior to allowance, the applicants communicated with the examiner six times. These communications are referred to as "A" through "F" in the district court's opinion and herein. The district court concluded that because of the prosecution history appellant is "prevented from construing its claims to include an internal anode." 658 F.Supp. at 587, 3 USPQ2d at 1577. We disagree.

The district court first relied on Amendments B and C. In the former, applicants inserted the limitation "only one of said connecting means applied to the skin surface of the living being" for the purpose of at

tempting to overcome a prior art rejection. This amendment was accompanied by remarks to the same effect. In Amendment C, this limitation was argued to be a distinguishing feature of the invention. Applicants' attempts to distinguish over the prior art in this fashion were unsuccessful, and the claims were later amended to remove this recitation. The arguments emphasizing the use of a skin electrode, which were made at the time the application claims explicitly contained such a limitation, cannot furnish a basis for restricting issued claim 1, which lacks any such limitation. *See Smith v. Snow* , 294 U.S. 1, 16 (1935) ("It is of no moment that in the course of the proceedings in the Patent Office the rejection of narrow claims was followed by the allowance of the broader Claim 1."); *Kistler Instrumente AG v. United States* , 628 F.2d 1303, 1308, 211 USPQ 920 (Ct. Cl. 1980) (*aff'g* and adopting 203 USPQ 511, 511) (courts are not permitted to read "back into the claims limitations which were originally there and were removed during prosecution of the application through the Patent Office.")

In Amendment D a claim which ultimately issued as independent claim 1 was submitted for the first time. In holding claim 1 should be limited to a skin anode, the district court relied on Amendments E and F which contained arguments relative to a skin anode and which were held by the district court to be in support of the claims that finally issued. 2 From Amendment F the district court quoted the following language:

Applicants take strong exception to [the examiner's] analysis of the [Friedenberg-Kohanim article]. Nowhere in this article is there either stated or suggested that one of the electrodes need simply be applied to the surface and the other introduced into the fracture site.

These remarks were submitted to correct the examiner's characterization of a prior art reference (an article written by one of the co-inventors of the patented invention). The examiner's characterization of the reference was made in rejecting claims, at least some of which included an explicit recitation of a surface anode. Thus, these remarks are of little significance.

The district court also noted the following argument in Amendment F:

Applicants throughout the prosecution of this case have repeatedly attempted to convey to the Examiner the important differences between their technique where only one of the electrodes need pierce the skin *and enter the fracture site* and the other prior art arrangements where two electrodes have to pierce the skin *and then fit into prescribed locations formed in the bone structure* under study. (Emphasis added.)

The quoted language does not mean that one electrode must remain on the surface of the skin. Rather, as applicants argue, it means that both of their electrodes do not have to be placed in the bone structure itself. The district court erred in construing the phrase "only one of the electrodes need pierce the skin" to mean that the other electrode must remain on the surface. This phrase, when read in conjunction with the words that follow -- "and enter the fracture site" -- only serves to distinguish prior art where both electrodes were placed in the bone structure. 3 The entire emphasis of the prior art article was that the electrodes were placed in the bone for the purpose of attempting to lengthen the bone. The article was not concerned with the healing of fractures or bone defects. In the healing of fractures, it is not necessary (or desirable) to place both electrodes in the bone.

[2] D. "There is presumed to be a difference in meaning and scope when different words or phrases are

used in separate claims. To the extent that the absence of such difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that the difference between claims is significant." *Tandon Corp. v. United States Int'l Trade Comm'n* , 831 F.2d 1017, 1023, 4 USPQ2d 1283, 1288 (Fed. Cir. 1987). "Where some claims are broad and others narrow, the narrow claim limitations cannot be read into the broad whether to avoid invalidity or to escape infringement. *Uniroyal, Inc* ., 837 F.2d at 1054-55, 5 USPQ2d at 1441 (quoting *D.M.I., Inc. v. Deere & Co* ., 755 F.2d at 1574, 225 USPQ at 239.

In this case the district court erroneously construed claim 1 so that its limitations are

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the same as dependent claim 2. Claim 2 reads in its entirety: "The system as defined in claim 1 wherein said connecting means includes means for external application to the skin surface, the internal means being a cathodic electrode, the external means being an anodic electrode." The doctrine of claim differentiation, therefore, counsels against limiting claim 1 to the use of a skin anode. *See D.M.I., Inc* ., 755 F.2d at 1574, 225 USPQ at 239.

E. On the basis of the above analysis, we conclude that the district court erred as a matter of law in its interpretation of claim 1 of the '841 patent. *Fromson v. Advance Offset Plate, Inc* ., 720 F.2d 1565, 1569, 219 USPQ 1137, 1140 (Fed. Cir. 1983).

The ordinary and accustomed meaning of claim 1 is that the current should be applied so as to avoid the formation of fibrous tissue. In support of this means plus function claim, the specification of the '841 patent disclosed both an implanted and a surface anode structure. The other claims, the specification and the prosecution history do not require a narrower construction. Thus, the district court erred in limiting claim 1 to the use of a skin anode.

II. *Literal Infringement*

The question of literal infringement is a factual inquiry. *Uniroyal, Inc. v. Rudkin-Wiley Corp* ., 837 F.2d at 1054, 5 USPQ2d at 1441. Literal infringement requires that every limitation of the patent claim must be found in the accused device. *Mannesmann Demag Corp. v. Engineered Metal Prods. Co* ., 793 F.2d 1279, 1282, 230 USPQ 45, 46 (Fed. Cir. 1986). In this case, the findings of the district court establish literal infringement and, thus, there is no need to remand for a determination of the factual question of infringement under properly interpreted claims.

[3] The district court stated in its opinion that:

The defendant's denial of infringement in this case is based solely on the defendants' anode and case being used internally. Accordingly the critical question in the case is whether the language of claim 1 (and with it the dependent claims) is limited to a skin anode.

As we have held in I., *supra* , the properly construed claims encompass both a skin anode and an implanted anode. The district court erroneously limited the claims of the '841 patent to a surface anode. Accordingly, on the position of Telectronics as stated by the district court, literal infringement is established.

The government also challenges the district court's finding of no infringement under the doctrine of equivalents. Because the accused devices literally infringe, a doctrine of equivalents inquiry is unnecessary. *See ZMI Corp. v. Cardiac Resuscitator Corp* ., 844 F.2d at 1581, 6 USPQ2d at 1562 ("When literal infringement is not found, the equitable doctrine of equivalents comes into play.").

III. *Invalidity*

The district court held: "[i]f claim 1 were to be given the broad meaning which plaintiff asserts, then the patent would be invalid for a failure to comply with the specification requirements of 35 U.S.C. §112." 658 F.Supp. at 589, 3 USPQ2d at 1577-78. According to the district court a dose response study must be performed for materials other than stainless steel to determine the optimal electrical current to be supplied and this would involve "an undue amount of experimentation." *Id* .

In its cross-appeal Telectronics argues that the patent is invalid for non-enablement regardless of how

the claims are interpreted because the disclosure does not bear a reasonable relationship to the scope of the claims.

Enablement is a legal determination which is reviewed as a matter of law. *Raytheon Co. v. Roper Corp .*, 724 F.2d 951, 951-60, 220 USPQ 592, 599 (Fed. Cir. 1983). To be enabling under section 112, the patent must contain a description sufficient to enable one skilled in the art to make and use the claimed invention. *Id .* A patent may be enabling even though some experimentation is necessary; the amount of experimentation, however, must not be unduly extensive. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co .*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). A patent is presumed valid, and the burden of proving invalidity, whether under section 112 or otherwise, rests with the challenger. Invalidity must be proven by facts supported by clear and convincing evidence. *Ralston Purina Co. v. Far-Mar-Co., Inc .*, 772 F.2d 1570, 1573-74, 227 USPQ 177, 178 (Fed. Cir. 1985) ("A party asserting invalidity based on 35 U.S.C. §112 bears no less a burden . . . than any other patent challenger.") Thus, although not mentioned by the district court it is Telectronics' burden to show by facts supported by clear' and convincing evidence that the patent was not enabling.

We note first that Telectronics admits that "[t]he patent *does* disclose how to successfully practice the invention -- if stainless

steel electrodes and a current in the range of 5-20 microamperes is [sic] used." (Emphasis in original.) Lack of enablement is asserted on the basis that "the claims are not limited to the specific metal/current combination."

The district court thought that to determine the optimal electrical current for materials other than stainless steel a dose response study would be required and that this would involve an "undue amount of experimentation." The district court said "the patent does not tell a person reasonably skilled in the art how to make and use this invention because it fails to teach how to select a level of current to promote bone formation and avoid fibrous tissue . . . formation from such current" for electrodes made of materials other than stainless steel. 658 F.Supp. at 589, 3 USPQ2d at 1578. It noted that "the patent does not contain an adequate description of the methodology for a dose response study for any cathode material other than stainless steel" and that "only those who were expert in the field and actually working with bone, doing electrical stimulation experiments . . . would know how to conduct" such a study. Moreover, the district court thought that the time and expense of such a study also indicated undue experimentation would be required.

[4] We are convinced that these findings and conclusions are insufficient to constitute clear and convincing proof of invalidity. First, it is undisputed that the patent disclosures are enabling with respect to stainless steel electrodes, with the range of current for such electrode set out in the specification. The specification shows this range of current was obtained by a dose response test. Next, according to the district court "those who were expert in the field and actually working with bone, doing electrical stimulation experiments . . . would know how to conduct a dose response study to determine the appropriate current to be used with other materials as electrodes." *Id .* The appropriate levels of current for other electrodes to promote bone growth and avoid fibrous tissue could, therefore, be determined. Finally, the emphasis by the district court on the time and cost of such studies is misplaced. While these factors may be taken into account, in the circumstances of this case we are unpersuaded that standing alone they show the experimentation to be excessive. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Hybritech Inc. v. Monoclonal Antibodies, Inc .*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied* , 107 S.Ct. 1606 (1987). Since one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation. *See SRI Int'l v. Matsushita Elec. Corp. of America* , 775 F.2d 1107, 1121, 227 USPQ 577, 586 (Fed.Cir. 1985) (the law does not require

an applicant to describe in his specification every conceivable embodiment of the invention); *Hybritech Inc* ., 802 F.2d at 1384, 231 USPQ at 94 (the enablement requirement may be satisfied even though some experimentation is required). While perhaps fortuitous, as the district court found, the OSTEOSTIM device of Telectronics used a current level of 20 microamperes, within the "substantially 5 microamperes to substantially 20 microamperes" range set forth in claim 5 and disclosed in the specification.

The district court also held that if claim 1 is read to mean that the current must be applied so as to minimize fibrous tissue formation then it would be invalid under 35 U.S.C. §112 (1982) because it would be "impossible to determine when sufficient minimization takes place to determine what current range is involved." 658 F.Supp. at 589, 3 USPQ2d at 1578. The district court erred as a matter of law in this holding. *Shatterproof Glass Corp. v. Libby-Owens Ford Co* ., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), *cert. dismissed* , 106 S.Ct. 340 (1985). Section 112, ¶2, requires only reasonable precision in delineating the bounds of the claimed invention. *Id* . Adjusting current so as to minimize fibrous tissue formation in other parts of the living being reasonably apprises those skilled in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *See id* . Thus, we hold as a matter of law that the '841 patent is enabling and that the claims satisfy 35 U.S.C. §112, ¶2.

In its cross appeal, Telectronics argues that the specification is enabling only for the use of stainless steel while the claims are not limited in the types of material from which the electrodes can be made. It contends that the scope of the protection must bear a reasonable relationship to the scope of enablement, citing *In re Fisher* , 427 F.2d 833, 838-39, 166 USPQ 18, 23-24 (CCPA 1970) ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved."),

and *In re Bowen* , 492 F.2d 859, 861-64, 181 USPQ 48, 50-52 (CCPA 1974) (section 112 requires that the scope of claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art). *Fisher* and *Bowen* both involved chemical reactions, recognized by our predecessor court as having a high degree of unpredictability and therefore requiring an increased enablement disclosure. Yet, in *Bowen* the board's non-enablement rejection was reversed where the "claims literally comprehend numerous polymers in addition to the one specifically described in appellant's specification" because no persuasive reason was given by the Patent Office why the specification does not realistically enable one skilled in the art to practice the invention as broadly as it is claimed. *In re Bowen* , 492 F.2d at 863, 181 USPQ at 51-52. The same can be said here. The only impediments are the time and cost of a dose response study, which the district court found could be performed by "those who were expert in the field and actually working with bone, doing electrical stimulation experiments . . . , " i.e., those skilled in the art. Moreover, as we have noted, Telectronic's device using different electrode materials actually operated within the current parameters disclosed in the specification.

We conclude that the district court erred in its nonenablement conclusion and that facts supported by clear and convincing evidence of invalidity were not adduced.

In view of our decision, we need not consider the district court's denial of attorney fees to Telectronics.

Costs

The parties shall bear their respective costs.

AFFIRMED-IN-PART AND REVERSED-IN-PART

Footnotes

Footnote 1. Telectronics has not appealed the district court's holdings on other issues it raised below.
Footnote 2. There was some uncertainty as to which set of claims certain of these remarks applied, but the district court found that Amendments E and F related to the claims presented in Amendment D. Because we conclude that the district court erroneously limited the claims even if the remarks in controversy did apply to the claims which issued, we need not determine whether the district court correctly resolved this dispute.
Footnote 3. The district court recognized that "[t]here are three possible positions for placement of the anode: on the skin, in soft tissue, and in the bone. Placement within the bone must be done carefully to avoid the effect of insulation from the cortical bone." 658 F.Supp. at 583, 3 USPQ2d at 1573.

- End of Case -
